IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Christoph Hehrlein et al.
Serial No.:	10/038,468
Filed:	01/03/2002
For:	DELIVERY SOURCE OF OXYGEN
Group Art Unit:	3763
Examiner:	Loan Thanh
Attorney's Docket No.:	OXIRA-1

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Commissioner for Patents

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Sir:

DECLARATION OF DR. ADALBERT KOVACS UNDER 37 CFR 1.132

The undersigned, Adalbert Kovacs, in support of the above-identified patent application, hereby states as follows:

1. My name is Adalbert Kovacs, I was born in Sighet, Romania, I currently reside at Maria-Montessori-Str. 41, 69221 Dossenheim, Germany, and I am a citizen of the Federal Republic of Germany.

2. I have B.Sc. in Chemistry from the Technical University of Darmstadt in Darmstadt, Germany.

3. I have an M.Sc. in Physical Chemistry from the University of Heidelberg in Heidelberg, Germany.

4. I have a Ph.D. in Physical Chemistry from the University of Heidelberg in Heidelberg, Germany.

5. During the course of my career, I have held various research positions, including at the University of Heidelberg, at the Steinbeis Transfer Center for Surface Technology and Surface Analysis in Heidelberg, Germany, and at Limedion GmbH of Mannheim, Germany.

6. I have had extensive training in the fields of Surface Technology (chemical vapor deposition, physical vapor deposition, polymers, ceramics, metals and corrosion), Surface Modification (ion implantation, ion beam assisted deposition and

electrochemical etching), and Surface Analysis (XPS, AES, XRD, SEM, AFM, IR, confocal laser microscopy and electrochemical analysis).

7. I have done extensive work in the field medical devices, and particularly with respect to medical devices for tissue oxygenation.

8. My doctoral thesis was entitled "Oxygen Releasing Coatings for Medical Devices".

9. I have published at least five scientific articles, and am an inventor on at least six patent applications.

10. I am currently the Chief Executive Officer of Limedion GmbH of Mannheim, Germany..

11. I am an inventor in the above-identified patent application.

12. I have reviewed all of the claims currently pending in the above-identified patent application (i.e., claims 35-57, which were introduced in the Request For Continued Examination and Amendment filed on October 31, 2007).

13. I have reviewed all of the prior art currently of record in this case, including U.S. Patent Nos. 5,084,011 (Grady); 6,146,358 (Rowe); and 5,334,142 (Paradis), all of which were applied by the Examiner in the Final Official Action issued October 12, 2006 (which is the last action by the Examiner prior to Applicants' filing a Notice of Appeal on April 5, 2007; an Appeal Brief on May 15, 2007; and then the Request For Continued Examination and Amendment filed on October 31, 2007).

14. I believe that none of the prior art currently of record in this case either discloses, or renders obvious, the subject matter of the claims currently pending in the above-identified patent application.

15. The claims currently pending in the above-identified patent application consist of three independent claims (i.e., claims 35, 56 and 57) and 19 dependent claims (i.e., claims 36-55).

16. All of the currently-pending independent claims call for, among other things, the provision of a hollow tube or a coronary wire; at least a portion of the hollow tube or the coronary wire comprising a porous membrane; and an oxygenated fluorocarbon solution incorporated in the porous membrane; wherein the porous membrane has a porosity in the range of 20-200 microns.

17. More specifically, independent claim 35 currently reads as follows:

35. A system comprising:

a *hollow tube* having a distal end, a proximal end, and a lumen extending between the distal end and the proximal end;

at least a portion of the tube comprising a *porous membrane;* and

an *oxygenated fluorocarbon solution incorporated in the porous membrane;*

wherein the porous membrane has a *porosity in the range of 20-200 microns,* in order that:

(i) the oxygenated fluorocarbon solution is effectively incorporated into the porous membrane; and

(ii) when the porous membrane is positioned in blood, the oxygenated fluorocarbon solution elutes out of the porous membrane, with the elution of the oxygenated fluorocarbon solution into the blood varying between minutes and several hours, depending on the temperature of the environment. (italics added for emphasis)

18. Independent claim 56 currently reads as follows:

56. (New) A system comprising:

a *coronary wire;*

at least a portion of the coronary wire comprising a *porous membrane;* and

an *oxygenated fluorocarbon solution incorporated in the porous membrane;*

wherein the porous membrane has a *porosity in the range of 20-200 microns,* in order that:

(i) the oxygenated fluorocarbon solution is effectively incorporated into the porous membrane; and

(ii) when the porous membrane is positioned in blood, the oxygenated fluorocarbon solution elutes out of the porous membrane, with the elution of the oxygenated fluorocarbon solution into the blood varying between minutes and several hours, depending on the temperature of the environment. (italics added for emphasis)

19. Independent claim 57 currently reads as follows:

57. A method for treating a patient, comprising:

providing:

(i) a *hollow tube* having a distal end, a proximal end, and a lumen extending between the distal end and the proximal end, at least a portion of the tube comprising a porous membrane; and

(ii) an *oxygenated fluorocarbon solution;*

loading the oxygenated fluorocarbon solution into the porous membrane; and

positioning the tube in the vascular system of the patient so that porous membrane is exposed to blood;

wherein the porous membrane has a *porosity in the range of 20-200 microns*, in order that:

(i) the oxygenated fluorocarbon solution is effectively incorporated into the porous membrane; and

(ii) when the porous membrane is positioned in blood, the oxygenated fluorocarbon solution elutes out of the porous membrane, with the elution of the oxygenated fluorocarbon solution into the blood varying between minutes and several hours, depending on the temperature of the environment. (italics added for emphasis)

20. The construction recited in these claims is a new and non-obvious advance over the prior art.

21. Among other things, and as will hereinafter be discussed in detail below, provision and use of a porous membrane having a particular pore size is a significant feature of the present invention, since it allows the oxygenated fluorocarbon solution to enter the bloodstream directly, without requiring the use of emulsifiers to prevent embolisms. This is a dramatic advance over the prior art.

22. More particularly, oxygenated perfluorocarbon (PFC) emulsions have been used to treat ischemic and hypoxic disorders. Oxygenated perfluorocarbon (PFC) emulsions became known as artificial blood substitutes more than twenty years ago. By way of example, in U.S. Patent No. 3,958,014 (Watanabe et al.) and U.S. Patent No. 4,252,827 (Yokoyama et al.), perfluorocarbon (PFC) emulsions are disclosed that have a small particle size of 0.02 microns to 0.25 microns, and which were injected into the blood stream. Additionally, U.S. Patent No. 4,445,500 (Osterholm) teaches that oxygenated perfluorocarbon emulsions can be injected into the cerebrospinal pathway to improve aerobic respiration of tissue. Furthermore, U.S. Patent No. 4,795,423 (Osterholm) discloses an intraocular perfusion with perfluorinated substances to treat ischemic retinopathy.

23. Unfortunately, clinical experience has shown that the prior art approaches for using PFC solutions are highly problematic. More particularly, and as will hereinafter be discussed in further detail, the prior art approaches for using PFC solutions prevent the

use of pure PFC solutions and, instead, require the use of PFC emulsions. These emulsions themselves introduce a new set of problems, thereby limiting the clinical utility of the PFC solutions.

24. More particularly, a pure PFC solution, with or without oxygen saturation, cannot be safely injected directly into the arterial or venous bloodstream, e.g., using a standard intravenous (IV) line or syringe. This is because introducing pure PFC solutions in such a manner creates embolisms in the blood. These embolisms are created due to the fact that PFC is hydrophobic and is not soluble in blood. Thus, when the PFC is injected directly into the bloodstream for hyperoxic medical therapy, the PFC tends to aggregate into relatively large bodies within the bloodstream. These relatively large aggregations of PFC (with or without oxygen) tend to create embolisms in the bloodstream. For this reason, introducing pure PFC (with or without oxygen) directly into the bloodstream, without the provision of a dispersion mechanism, is not feasible due to the creation of embolisms.

25. Furthermore, it is not possible to eliminate the problematic PFC aggregations by diluting the PFC with another liquid prior to its introduction into the bloodstream, because PFC is not easily soluble in biocompatible fluids (e.g., PFC is insoluble in saline). Thus, the PFC tends to re-aggregate even when it is diluted with another liquid.

26. As a result, and as noted above, emulsifying agents (such as egg yolk phospholipids, Pluronic-F68 and other emulsifiers) have traditionally been added to the PFC prior to injection of the PFC into the bloodstream, whereby to minimize aggregations of the PFC within the bloodstream. See, for example, U.S. Patent Nos. 3,958,014 (Watanabe et al.); U.S. Patent No. 4,252,827 (Yokoyama et al.); 4,445,500 (Osterholm); and 4,795,423 Osterholm). However, clinical studies in humans evaluating such PFC emulsions (i.e., Fluosol and others) have shown that the use of these emulsions, infused into blood with the PFC for hyperoxic therapy, can cause respiratory insufficieny and pulmonary edema (Wall TC et al., Circulation 1994) most likely by mechanisms of fluid overload and subsequent congestive heart failure. Thus, PFC emulsions can be considered as PFC particles that are generally accompanied by large quantities of another therapeutic agent to emulsify the pure PFC solution However, these large quantities of additional therapeutic agent in turn significantly increase intravascular volumes and thereby induce unwanted side-effects.

27. In addition, PFC emulsions can upload and release far less oxygen than a pure PFC solution. Thus, where emulsifiers are added to the PFC, Kim et al. showed it was required to provide additional systemic oxygenation via the lung by breathing 100% oxygen so as to create a sufficiently therapeutic oxygen tension of the PFC emulsions. This is a situation to be avoided clinically due to the adverse effects of elevated oxygen concentration on the lungs (e.g., oxygen toxicity) (Kim HW et a., Artificial Organs, Vol 28, No.9 2004).

28. Moreover, the use of emulsions to disperse PFC through the blood may cause allergic reactions. Mattrey et al. showed that PFC emulsions can cause allergic reactions. In an investigation of Fluosol-DA 20% as a contrast agent using Pluoronic-F68 and others as emulsifers for PFC in humans, it was reported that Fluosol-DA 20% caused allergic reactions which are most likely triggered by complement activation of the substance Pluronic-F68 (Mattrey RF et al., Radiology 1987). Since pure PFCs are chemically inert and contain no emulsifiers, no allergic reactions are to be expected when using pure PFCs in the blood.

29. For these reasons, using oxygenated PFCs in conjunction with emulsifiers to prevent hypoxia has not heretofore been clinically successful.

30. Thus it will be seen that pure PFCs cannot be introduced directly into the bloodstream without some dispersive mechanism to prevent embolisms. However, it will also be seen that using PFC emulsions as the dispersive mechanism introduces a new set of problems which can have dire consequences.

31. For these reasons, prior art PFC systems have not been clinically successful.

32. As a result of previously reported clinical studies and through our independent research efforts, my co-inventors and I concluded that the best approach for using PFCs in the body would be to utilize a pure PFC solution in order to eliminate the aforementioned clinical complications associated with emulsifiers, but that we would need to develop a radically new (i.e., non-emulsifier) dispersive mechanism to prevent the formation large PFC aggregations in the bloodstream and hence the occurrence of embolisms.

33. It was our subsequent efforts to develop a new dispersive mechanism for pure PFC solutions which led to the present invention.

34. More particularly, in the course of our efforts, we discovered that it is possible to use a carefully constructed porous membrane (which may also be referred to as a porous substrate) to safely dispense pure, chemically inert PFCs directly into the bloodstream at sufficiently low rates, and in sufficiently small bodies, to prevent the creation of the aforementioned large PFC aggregations which lead to embolisms.

35. More particularly, we have discovered that our carefully constructed porous membrane may be mounted on a catheter or coronary wire, pure PFC loaded into the porous membrane, the catheter or coronary wire advanced into the vascular system of the patient so that the porous membrane is located at a selected site within the bloodstream, and the porous membrane will act as a dispersion mechanism to dispense

pure PFC liquid directly into the bloodstream - in a carefully controlled, highly dispersed manner - so that micro-, nano-, and subnano- sized quantities of PFC molecules safely enter the bloodstream, without the occurrence of large PFC aggregations and the resulting embolisms.

36. An important aspect of the present invention is that the porous membrane must be carefully constructed so as to permit the oxygenated PFC to enter the bloodstream at the appropriate rate. In fact, we have discovered that it is important to form the porous membrane with a porosity which permits the oxygenated PFC to disperse into the bloodstream in very small volumes, and at a highly controlled rate, which is both (i) sufficiently high to provide therapeutic benefit by the delivery of adequate therapeutic oxygen molecules to tissue, and (ii) sufficiently low so as to avoid the creation of fluid overload and/or embolisms in the bloodstream, even when using pure PFCs.

37. In practice, we have found that for a catheter or coronary wire placed into an artery having a substantially normal rate of bloodflow, forming the porous membrane with a porosity in the range of 20-200 microns permits appropriate dispersion of the oxygen-rich PFC into the bloodstream.

38. Our research suggests that a pore size of greater than 200 microns will increase the likelihood of embolism.

39. Our research also suggests that a pore size of less than 20 microns makes it difficult to deliver enough oxygen to a site to provide a significant therapeutic benefit.

40. In practice, we have found that a pore size of 20-200 microns provides excellent therapeutic benefit while still preventing the creation of embolisms.

41. Thus, in one aspect of the present invention - and in all of the claims currently pending in the present patent application - we call for, among other things, the provision of a hollow tube or a coronary wire; at least a portion of the hollow tube or the coronary wire comprising a porous membrane; and an oxygenated fluorocarbon solution incorporated in the porous membrane; wherein the porous membrane has a porosity in the range of 20-200 microns.

42. None of the prior art currently of record either discloses or renders obvious such a construction.

43. In the Final Official Action issued October 12, 2006, the Examiner relied upon U.S. Patent Nos. 5,084,011 (Grady), 6,146,358 (Rowe) and 5,334,142 (Paradis) to reject the claims then pending in the application.

44. A thorough reading of Grady reveals that the only mention of "fluorocarbon" is in relation to the prior art reporting an infant *breathing* fluorocarbon

liquid which was oxygenated with pure oxygen. The Grady reference is totally silent with regard to the presence of an elutable oxygenated fluorocarbon solution which is incorporated into a porous substrate, and introducing that combination directly into the bloodstream in order to *intravascularly* oxygenate tissue.

45. The Rowe reference relates to a balloon catheter having, on a portion of its surface, a mixture comprising a therapeutic agent and a release carrier, where the release carrier comprises microparticles, etc., with the mixture being delivered to a localized internal tissue site of the patient. Rowe does not teach the provision of a porous substrate, nor does he teach the provision of an elutable fluorocarbon solution.

46. Paradis teaches an oxygenated fluorocarbon solution to infuse the aorta distal to a balloon occlusion. However, the oxygenated fluorocarbon solution of Paradis is infused directly into the bloodstream. Therefore, Paradis must be using an emulsified PFC solutions or risk the occurrence of potentially-fatal embolisms. There is no teaching in Paradis of Applicants' use of a carefully constructed porous membrane to provide a highly controlled dispersion of the PFC into the bloodstream, thereby making it possible to use a pure PFC solution without the risk of embolisms.

47. Thus it will be seen that none of the prior art of record, taken either alone or in combination with one another, discloses or renders obvious our claimed invention, which calls for, inter alia, the provision of a hollow tube or a coronary wire; at least a

portion of the hollow tube or the coronary wire comprising a porous membrane; and an oxygenated fluorocarbon solution incorporated in the porous membrane; wherein the porous membrane has a porosity in the range of 20-200 microns.

48. On account of the foregoing, Applicants submit that claims 35-57 are patentable over the prior art of record. Early and favorable reconsideration is therefore respectfully requested.

49. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

28th December 2007

Date

Adalbert Kovacs, Ph.D.

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